REMARKS

Status of the Claims

Claims 1-10, 12-21, 23-26, 36, 49-52 and 58-67 are in the application.

Claims 9 and 21 have been withdrawn from consideration.

Claims 1-8, 10, 12-20, 23-26, 36, 49-52 and 58-67 were rejected.

Claims 1, 4-6 and 10 have been amended, claim 7 has been canceled and new claims 68-74 have been added.

Upon entry of this amendment, claims 1-6, 8-10, 12-21, 23-26, 49-52 and 58-74 will be pending.

Please amend claims cancel claim 7, and add new claims.

Summary of the Amendment

Claim 1 has been amended to delete duplicative language and delete reference to, tricarboxylate transporter inhibitor, the non-elected alternative to citrate lyase inhibitor.

Claims 1 and 10 have each been amended to more specifically set forth the effect of the administration of the citrate lyase inhibitor. As amended, claims 1 and 10 require that the amount of citrate lyase inhibitor administered to the individual be sufficient to inhibit ATP citrate lyase activity in the cancer cell to result in sufficient inhibition of conversion of citrate into oxaloacetic and acetyl-CoA in said cancer cells such that hyperpolarization of mitochondria and increased reactive oxygen species production occurs at a level sufficient to cause the cells to undergo apoptosis As amended, claims 1 and 10 expressly state that the amount of citrate lyase inhibitor must be sufficient to kill the cancer cells by a specific mechanism that occurs as the result of citrate lyase inhibition. As amended, claims 1 and 10 continue to read on the elected species. Support for the amendment is found throughout the specification such as the paragraph bridging pages 4 and 5.

Claims 4-6 have been amended to correct obvious typographical errors.

Claim 7 has been canceled as being redundant with claim 10 in view of the amendment of claim 1.

Claim 16 has been amended to more specifically set forth the effect of the administration of the citrate lyase inhibitor and tricarboxylate transporter inhibitor. As amended, claim 16 requires that the amount of citrate lyase inhibitor and tricarboxylate transporter inhibitor administered to the individual be sufficient to inhibit transport and conversion of citrate into oxaloacetic and acetyl-CoA in said cancer cells such that hyperpolarization of mitochondria and increased reactive oxygen species production occurs at a level sufficient to cause the cells to undergo apoptosis As amended, claims 16 expressly state that the amount of the two inhibitors must be sufficient to kill the cancer cells by a specific mechanism that occurs as the result of blocking citrate lyase transport and activity. As amended, claim 16 continues to read on the elected species. Support for the amendment is found throughout the specification such as the paragraph bridging pages 4, 5 and 10.

Claim 52 has been amended to delete reference to the inhibition of tricarboxylate transporter expression, the non-elected alternative to inhibition of citrate lyase expression. In addition, claim 52 has been amended to explicitly recite that the inhibition of citrate lyase expression sufficient to inhibit ATP citrate lyase activity in the cancer cell to result in sufficient inhibition of conversion of citrate into oxaloacetic and acetyl-CoA in said cancer cells such that hyperpolarization of mitochondria and increased reactive oxygen species production occurs at a level sufficient to cause the cells to undergo apoptosis. As amended, claim 52 continues to read on the elected species. Support for the amendment is found throughout the specification such as the paragraph bridging pages 4 and 5.

New claims 68, 72 and 74 have been added to refer to specific cancers in addition to glioma. New claims 68, 72 and 74 read on the elected species. Support for new claims 6, 72 and 74 is found throughout the specification such as on pages 27-29.

No new matter has been added.

Claim Rejection Under 35 U.S.C. § 103(a)

Claim 1-8, 10, 12-15, 50-52 and 58-65 stand rejected under 35 USC 103(a) as unpatentable over Kuhajda et al. (US Patent No. 5, 759,837) in view of Schroder et al (1999 Int. J. Gynecol Cancer).

Kuhajda et al. discloses methods of treating individuals who have **cancer that is dependent on endogenously synthesized fatty acid.** According to Kuhajda et al. inhibition of fatty acid synthesis in such cancer cells can selectively eliminate such cells. Among the targets for inhibiting fatty acid synthesis disclosed by Kuhajda et al is citrate lyase. Kuhajda et al teaches inhibiting citrate lyase in cancer cells dependent on endogenously synthesized fatty acid sufficient to inhibit fatty acid synthesis.

Schroder et al discloses use of PET to detect metastatic ovarian tumors.

It had been asserted that it would have been obvious to combine the teaching of Kuhajda et al and Schroder et al. to produce the present invention. In response to applicants' previous arguments, the Office indicates that the reasons to combine references does not have to be done for the same reasons as those that led to the present invention. Applicants respectfully urge reconsideration of the rejection.

Kuhajda et al. discloses methods of treating individuals who have cancer that is dependent on endogenously synthesized fatty acid. The instant invention relates to treating individuals who can cancer identified as comprising cancer cells that have a high rate of aerobic glycolysis. While in some cases overlapping, these two groups of patients are not the same group. Not all cancer cells that are dependent on endogenously synthesized fatty acid have a high rate of aerobic glycolysis. Likewise, cancer cells that have a high rate of aerobic glycolysis are dependent on endogenously synthesized fatty acid. Claims 1, 10, 16 and 52 have been amended to recite that the inhibition of citrate lyase must be at a level that induces apoptosis due to insufficient processing of citrate which leads to mitochondrial hyperpolarization and an increase in reactive oxygen species production. That is, the amount of drug delivered is in an amount that causes cell death in cancer cells with a high rate of aerobic glycolysis by inhibition of a critical metabolic pathway. Cancer cells that do not have a high rate of aerobic

glycolysis are not susceptible to induction of apoptosis by inhibiting the level of citrate lyase activity sufficient to cause mitochondrial hyperpolarization and an increase in reactive oxygen species production. The metabolic pathway involving citrate lyase is not critical to cancer cells that do not have a high rate of aerobic glycolysis. Kuhajda et al. teaches to administer sufficient inhibitor to inhibit fatty acid synthesis. Thus, following the teachings of Kuhajda et al. one skilled in the art would not necessarily provide a sufficient dosage to an individual, even if the individual fell into the overlapping group of patients with cancer dependent on endogenously synthesized fatty acid and having a high rate of aerobic glycolysis. Kuhajda neither teaches nor suggests the claimed invention.

With respect to claims 10, 12-15 and 65, Applicants respectfully urge that Kuhajda teaches away from claimed invention. Kuhajda et al. discloses methods of treating individuals who have cancer that is dependent on endogenously synthesized fatty acid. Claim 10 states that the cancer cells in the individual to be treated "are not dependent on endogenously synthesized fatty acid". Claims 10, 12-15 and 65 are completely contrary to the teachings of Kuhajda.

Regarding Schroder, Applicants urge that Schroder teaches using PET to identify ovarian tumors. Claims 64, 65 and 66 refer to glioma. Attached hereto as Exhibits A, B and C are the references Schöder, H., et al., POSITRON EMISSION TOMOGRAPHY FOR PROSTATE, BLADDER, AND RENAL CANCER, Seminars in Nuclear Medicine, 2004, pp. 274-292; Cloran F. J, et al.,LIMITATIONS OF DUAL TIME POINT PET IN THE ASSESSMENT OF LUNG NODULES WITH LOW FDG AVIDITY, Lung Cancer, 2009, pp. 1-6; and Ullrich, R. T. et al.,NEUROIMAGING IN PATIENTS WITH GLIOMAS, Seminars in Neurology, Vol. 28, No. 4, 2008, pp. 484-494, respectively, which each disclose the limitations of the use of PET FDG as a technology for identifying specific tumors. Since not all tumors have a high rate of glycolysis and therefore take up glucose at a high rate, their detection using technology such as PET FDG is limited since PET FDG requires enhanced uptake of labeled glucose. In the case of glioma, PET FDG is useful despite high background.

The combination of Kuhajda et al and Schroder et al. does not produce the claimed invention. Accordingly, the claimed invention is not prima facie obvious over the combination.

Moreover, at the time the invention was made, one skilled in the art would not have modified the combined the teachings of Kuhajda et al and Schroder et al. to administer the amount of citrate lyase inhibitor in a dosage sufficient to inhibit of conversion of citrate into oxaloacetic and acetyl-CoA in the cancer cells such that hyperpolarization of mitochondria and increased reactive oxygen species production occurs at a level sufficient to cause the cells to undergo apoptosis Since the patient populations to be treated are not identical and the pathway to be inhibited is different, one skilled in the art could not use the teachings of Kuhajda et al. combined with Schroder et al. to make the necessary modifications to produce the claimed invention.

Regarding claims 10, 12-15 and 65, Kuhajda et al teaches away from the claimed invention and cannot be properly relied upon.

With regard to Schroder, contrary to the Office's assertion that PET would be used for routine cancer detection and imaging, when used with labeled glucose the technology is only useful to detect cancer cells with high levels of aerobic glycolysis. PET FDG is useful in the present invention because it is not simply detection of some tumors but rather it detects tumors susceptible to treatment with citrate lyase inhibitors. Detection of cancer cells with high levels of aerobic glycolysis such as through the use of PET FDG is a specific technology to identify cancer which can be treated according to the present invention. While PET FDG, or any other methodology useful to detect cancer cells with high levels of aerobic glycolysis has limited utility in cancer imaging since it only images those cancer cells with high levels of aerobic glycolysis and not those with other functional metabolic pathways.

Claim 1-6, 8, 10, 12-15, 50-52 and 58-65 and new claims 68-74 are not obvious in view of Kuhajda et al. and Schroder et al. Applicants respectfully request that the rejection of Claim 1-8, 10, 12-15, 50-52 and 58-65 under 35 USC 103(a) as unpatentable over Kuhajda et al. in view of Schroder et al. be withdrawn

Claim 1-8, 10, 12-20, 23-26, 36, 49-52 and 58-67 stand rejected under 35 USC 103(a) as unpatentable over Kuhajda et al. (US Patent No. 5, 759,837) in view of Schroder et al (1999 Int. J. Gynecol Cancer) and further in view of Bru et al. (US Patent No. 5,219,846).

Kuhajda et al. and Schroder et al. are discussed above.

Bru et al. is cited as teaching the use of phosphoenolpyruvic acid to treat tumors.

Claims 1, 10 and 52 have been amended to delete reference to tricarboxylate transporter inhibition and claim 7 has been canceled. Accordingly, the rejection as applied to claims 1-8, 10, 12-15, 49-52 and 58-65 is moot. Claims 16-20, 23-26, 36, 66, 67 and new claim 73 continue to require administration of a tricarboxylate transporter inhibitor.

It had been asserted that it would have been obvious to combine the teaching of Kuhajda et al and Schroder et al. and Bru et al. to produce the present invention. It is asserted that the use phosphoenolpyruvic acid as an anti-tumor agent as taught by Bru et al would have been obvious for additive effect with the use of citrate lyase inhibitors taught by Kuhajda et al in cancer patients identified according to the teachings of Schroder et al. Applicants respectfully urge reconsideration of the rejection.

As noted above, Kuhajda et al. discloses methods of treating individuals who have cancer that is dependent on endogenously synthesized fatty acid while the instant invention relates to treating individuals who can cancer identified as comprising cancer cells that have a high rate of aerobic glycolysis. Nothing in Kuhajda et al. teaches inhibiting citrate lyase at a level that induces apoptosis due to insufficient processing of citrate which leads to mitochondrial hyperpolarization and an increase in reactive oxygen species production. Likewise, nothing in Bru et al. suggests using phosphoenolpyruvic acid in combination with a citrate lyase inhibitor at levels that induce apoptosis due to insufficient transport and processing of citrate which leads to mitochondrial hyperpolarization and an increase in reactive oxygen species production.

Cancer cells that do not have a high rate of aerobic glycolysis are not susceptible to induction of apoptosis by inhibiting the level of citrate lyase activity sufficient to cause mitochondrial hyperpolarization and an increase in reactive oxygen species production. The metabolic pathway involving citrate lyase and tricarboxylate transport is not critical to cancer

cells that do not have a high rate of aerobic glycolysis. Following the teachings of Kuhajda et al. and Bru et al., one skilled in the art would not necessarily provide a sufficient dosage to an individual. Neither Kuhajda nor Bru et al. teach or suggest the claimed invention.

As noted above, Applicants urge that Schroder while teaching use PET to identify ovarian tumors, does not disclose glioma as set forth in claim 66. The attached references Exhibits A, B and C each disclose the limitations of the use of PET FDG as a technology for identifying specific tumors. Since not all tumors have a high rate of glycolysis and therefore take up glucose at a high rate, their detection using technology such as PET FDG is limited since PET FDG requires enhanced uptake of labeled glucose. In the case of glioma, PET FDG is useful despite high background.

The combination of Kuhajda et al, Schroder et al. and Bru et al does not produce the claimed invention. Accordingly, the claimed invention is not prima facie obvious over the combination. Moreover, at the time the invention was made, one skilled in the art would not have modified the combined the teachings of Kuhajda et al, Schroder et al. and Bru et al to administer the amount of citrate lyase inhibitor and tricarboxylate transport inhibitor in a dosages sufficient to inhibit the transport and conversion of citrate into oxaloacetic and acetyl-CoA in the cancer cells such that hyperpolarization of mitochondria and increased reactive oxygen species production occurs at a level sufficient to cause the cells to undergo apoptosis

Contrary to the Office's assertion that PET would be used for routine cancer detection and imaging, when used with labeled glucose the technology is only useful to detect cancer cells with high levels of aerobic glycolysis. PET FDG is useful in the present invention because it is not simply detection of some tumors but rather it detects tumors susceptible to treatment with citrate lyase inhibitors. Detection of cancer cells with high levels of aerobic glycolysis such as through the use of PET FDG is a specific technology to identify cancer which can be treated according to the present invention. While PET FDG, or any other methodology useful to detect cancer cells with high levels of aerobic glycolysis has limited utility in cancer imaging since it only images those cancer cells with high levels of aerobic glycolysis and not those with other functional metabolic pathways.

Claim 16-20. 23-26, 36, 66, 67 and new claim 73 are not obvious in view of Kuhajda et al., Schroder et al. and Bru et al. Applicants respectfully request that the rejection of Claim 1-8, 10, 12-20, 23-26, 36, 49-52 and 58-67 under 35 USC 103(a) as unpatentable over Kuhajda et al. in view of Schroder et al. and further in view of Bru et al. be withdrawn.

Conclusion

Claims 1-6, 8-10, 12-21, 23-26, 49-52 and 58-74 are in condition for allowance. A notice of allowance is earnestly solicited. Applicants invite the Examiner to contact the undersigned at 610.640.7855 to clarify any unresolved issues raised by this response.

The Commissioner is hereby authorized to charge any deficiencies of fees and credit of any overpayments to Deposit Account No. 50-0436.

Respectfully submitted,

/Mark DeLuca, Reg. No. 33,229/
Mark DeLuca
Registration No. 33,229

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PEPPER HAMILTON, LLP
400 Berwyn Park
899 Cassatt Road
Berwyn, PA 19312-1183
Telephone: 610-640-7855
Facsimile: 610-640-7835

Exhibit A: Schöder, H., et al., POSITRON EMISSION TOMOGRAPHY FOR PROSTATE, BLADDER, AND RENAL CANCER, Seminars in Nuclear Medicine, 2004, pp. 274-292

Exhibit A: Cloran F. J, et al.,LIMITATIONS OF DUAL TIME POINT PET IN THE ASSESSMENT OF LUNG NODULES WITH LOW FDG AVIDITY, Lung Cancer, 2009, p. 1-6

Exhibit C: Ullrich, R. T. et al.,NEUROIMAGING IN PATIENTS WITH GLIOMAS, Seminars in Neurology, Vol. 28, No. 4, 2008, pp. 484-494